White Paper

Inclusion of Obese Individuals in Early Phase Healthy Volunteer Trials

Considerations to optimize drug development

DAVID DUQUE, MD, Senior Director, Medical Strategy Lead, IQVIA Early Clinical Development Centre of Excellence

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Introduction

Traditionally, early-phase trials in healthy volunteers have enrolled individuals whose body mass index (BMI) falls within the 'normal' and 'overweight' ranges (18 to <30kg/m^2), but excluded those with a BMI within the 'obese' category (≥30kg/m^2). Non-obese subjects are preferred because they usually have fewer comorbidities and are thought to respond more consistently to Investigational Products, better suiting a 'healthy volunteer' profile. This preference has been seen with early-phase trials conducted by IQVIA in the past five years, approximately 43% of which excluded obese volunteers.

Nonetheless, there is an increasing trend for life sciences customers, clinical research units and investigators to ask to include participants with a BMI that falls within the obese range, commonly up to 32 kg/m^2 (as seen in 40% of IQVIA's recent early-phase trials). However, in some therapeutic areas, there have been requests to include individuals with a BMI as high as 42 kg/m^2.

Authored by an IQVIA expert, this white paper explores considerations for including participants defined as obese based on their BMI in early-phase clinical trials.

Background

Obesity – a chronic disease involving abnormal accumulation of adipose tissue, also known as fat tissue, defined by a BMI ≥30 kg/m^2 [1, 2, 3] – has almost doubled in global prevalence since 1990.[2] In 2022, 43% of adults worldwide were overweight;[2] in the United States, all states and territories had an obesity prevalence higher than 20%. Only seven US states had an obesity prevalence of less than 30%, with three states reporting a prevalence above 40%.[3]

Obesity is not just a change in weight at the expense of fat/adipose tissue; it involves multiple physiological changes, and is a major risk factor for comorbidities including cardiovascular disease, type 2 diabetes, musculoskeletal disorders and cancer.[1, 2] Obesity can also affect the pharmacokinetic profiles of a variety of medications and Investigational Products.[1, 4, 5, 6, 7]

Drug manufacturers traditionally do not assess the effects of obesity on the safety, pharmacokinetics or efficacy of their Investigational Products, and this can certainly be considered a shortcoming of the drug development process.[4]

Use of BMI and obesity classification

BMI is used by the World Health Organization (WHO), U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) and Centers for Disease Control and Prevention (CDC) to classify overweight and obesity in adults (a BMI ≥25 kg/m^2 and ≥30 kg/m^2 respectively).[1, 2, 3, 6] The use of BMI is frequently criticized as it fails to distinguish between adipose tissue and lean muscle mass[4, 6] and does not correspond to the same degree of fat accumulation among different individuals. However, BMI remains the most widely used metric for overweight and obesity gradation,[5] likely because of its ease of use, low cost, simplicity and reliability, and the fact that it also consistently correlates to clinical outcomes.[6]

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RACE AND BMI

There seems to be a markedly higher disease-related risk at the same BMI in some racial groups compared to others. For example, Asians have more than double the risk of developing type 2 diabetes as Caucasians at the same BMI.[9]

Certain Asian countries have their own overweight/obesity classifications; for example, China and Japan define a BMI ≥24 kg/m^2 as overweight and ≥28 kg/

m^2 as obese, while India defines a BMI ≥23 kg/m^2 as overweight and ≥27 kg/m^2 as obese.[9]

An argument can be made that the BMI classification should be race specific, and several calculators are available with a BMI classification that varies according to race, including examples from the British Heart Foundation and the Joslin Diabetes Center. However, the WHO has examined the evidence, specifically for Asians, and declined to set different cutoff points due to a lack of agreement among researchers.[9] As a result, a common BMI classification is still required to be used for all racial groups when defining obesity ranges.

Obesity and drug pharmacokinetics

Assessing safety and tolerability, and the characterization of a drug's pharmacokinetic profile, are the main objectives of early phase clinical trials. Obesity-related pathophysiological changes can substantially influence a drug's pharmacological profile, even in otherwise healthy individuals. Compared to normal weight control healthy individuals, this can affect not only the pharmacokinetic profile but potentially put subject safety at risk.[7]

ABSORPTION

Bioavailability of drugs may potentially be altered in obese patients depending on the method of administration.

Gastrointestinal transit as well as gastric emptying appears to be accelerated, which added to the increased gastric pH seen in obese people (and amplified by the potential use of acid reducing agents) could reduce the solubilization and absorption of some oral drugs, especially poorly water soluble drugs.[1] Obese individuals also have increased blood flow in the abdominal (splanchnic) organs that promotes paracellular absorption through the gastric wall and increases gut permeability. This improves drug bioavailability[1, 4, 5, 6] as has been reported for the oral route.[4, 5]

Drugs administered through the subcutaneous and transdermal routes can be affected by the significant increase in subcutaneous fat, where a reduced rate of absorption is reported.[4, 5] This is due to the dependency of these routes on the blood flow to the skin tissue and subcutaneous fat, which is significantly lower when compared to that of nonobese individuals (where it is already only 5% of the cardiac output for fat tissue).[5]

DISTRIBUTION

Obese individuals have an important quantitative increase in the volume of distribution for lipophilic drugs,[1, 4, 7] compared to a low or moderate increase for hydrophilic drugs. This can lead to their accumulation in fat tissue, with a half-life prolongation and a delay to reach steady state concentrations. This can also result in a storage-release (delayed washout) phenomena,[1, 5, 7] which can become a safety concern if they persist for too long, as demonstrated in pharmacokinetic drug-drug interaction (DDI) studies of posaconazole, lurasidone and ranolazine.[7]

The composition of tissue also determines the distribution of drugs, and for obese individuals the volume and mass of some tissues or organs increases at expense of fat tissue (such as the liver), while it remains the same for others (such as the brain, lungs, and spleen).[1,4]

METABOLISM

The liver of obese patients frequently presents fatty infiltration that is associated with Non-Alcoholic Fatty Liver Disease – ranging from liver steatosis to metabolic dysfunction-associated steatohepatitis (MASH), previously known as non-alcoholic steatohepatitis (NASH) – with an increased hepatic blood flow and liver volume.[1, 4]

Obese individuals have a decreased CYP3A4-dependent hepatic clearance, which is involved in breaking down more than 45% of metabolized drugs, including benzodiazepines, alfentanil and clopidogrel. These individuals conversely have a higher CYP2D6 clearance, which is involved in the breakdown of 25-30% of metabolized drugs, such as dexfenfluramine and nebivolol.[1, 4] With obesity, metabolism of drugs such as

acetaminophen may also be affected due to elevation of hepatic glucurono-conjugation. [1, 4]

EXCRETION

Obesity is associated with changes in kidney function, with increased renal perfusion and glomerular hyperfiltration,[5] and estimated glomerular filtration rates (eGFRs) increasing up to 62%.[4] However, this condition can ultimately lead to obesity-related glomerulopathy (proteinuria, glomerulomegaly, progressive glomerulosclerosis and reduction of the renal function) and chronic kidney disease.[1]

In general, studies have shown that the clearance of drugs eliminated by the kidneys is higher in obese individuals, likely due to increased glomerular filtration and tubular secretion.[4, 6] However, the renal function of obese patients is likely overestimated due to a decrease in creatinine production, glomerular hyperfiltration and the lack of accuracy of common eGFR formulas when used in obese people.[1]

Other relevant pathophysiological changes in obesity

LENGTHENING OF THE QT INTERVAL

Obesity has been associated with prolongation of QT interval among otherwise healthy young obese adults. This condition increases the possibility of left ventricular enlargement and ventricular fibrillation,[10] as obesity can frequently cause this QT abnormality due to hypertension, autonomic changes and cardiac remodeling; some studies show that QT interval shortens with weight loss.[11]

HYPERCOAGULABILITY

There is a known link between obesity and higher plasma concentrations of all pro-thrombotic factors, as well as with arterial and venous thrombosis, and various associated inflammatory changes.[13] Furthermore, obese individuals have shown higher rates of thromboembolic complications following injury, where BMI is a significant independent predictor of the development of these complications.[12]

CHRONIC LOW-GRADE INFLAMMATION

In recent years, a relationship between obesity, chronic low-grade inflammation and metabolic syndrome has been established.[14, 15, 16]

This inflammation has been observed in multiple tissues, including the liver, pancreas, visceral and subcutaneous adipose tissue, skeletal muscle, intestine, and brain.[16] This involves increased expression of proinflammatory factors such as TNFα and IL-6;[15, 16] and weight loss is associated with a reduction in levels of multiple inflammation biomarkers.[15, 16]

Regulatory landscape

There are currently no FDA guidances or regulations on how or when to investigate the safety and/or pharmacokinetic characterization of Investigational Products in obese subjects. This void should be addressed to help ensure their effective and safe use in obese individuals as part of the drug development process, allowing for possible dose adjustments.

RECENT EFFORTS

Both the FDA and the European Medicines Agency (EMA) have taken the first steps towards exploring when these investigations should be considered. These regulators have reviewed the implications of obesity for safety, efficacy, drug dosing and disposition, and discussed how to use these findings to create guidelines for the inclusion of obese patients in clinical trials and develop specific dosing recommendations. The EMA adopted a *"Reflection paper on investigation of pharmacokinetics in the obese population – Scientific guideline"* on December 4, 2023, which was first published on February 14, 2024,

[5] and the FDA held a virtual workshop titled, *"Bridging Efficacy and Safety to the Obese: Considerations and Scientific Approaches"* in November 2022.[6]

OBESITY AS PART OF DIVERSITY IN CLINICAL TRIALS VS. OBESITY AS A SPECIFIC PATIENT POPULATION

Ongoing efforts and mandates aim to address the underrepresentation of minorities in clinical trials, promoting the inclusion of members of traditionally excluded groups to help reduce health disparities. A case has been presented that obese individuals are an underrepresented population akin to racial, ethnic and gender diversity, with a call for their inclusion in all phases of clinical development and for modification of the National Institutes of Health (NIH) Revitalization Act.[8]

Others, approaching obesity as a disease, deem that obese individuals should instead be considered as a special population, and should be studied in a similar way to patients with renal or hepatic impairment. This approach is supported by the pathophysiological and pharmacological considerations mentioned in this paper, and it is currently the approach favored by most opinion leaders.[1, 6]

THE FUTURE

The adoption of an EMA guideline on investigation of pharmacokinetics in the obese[5] is a step forward, with a need for similar action by other regulatory agencies. New guidance and regulations for the inclusion of obese individuals in clinical trials will ultimately result in appropriate treatment recommendations, ensuring that obese patients receive treatments that are as effective and safe as for the general non-obese target population.[5] Clear definitions are needed of when it is necessary to investigate the effects of obesity in the clinical development plan of new therapies.

There is general consensus that, when needed, the inclusion of obese participants should start as early as possible in drug development,[5, 6] but should not be mandatory for every investigational product. In silico modeling and population pharmacokinetic analysis (also known as PopPK) can be efficient and accurate tools to make predictions as to which drugs would need assessment in obese individuals.[5, 6] This would avoid the addition of unnecessary costs to product development and putting further burden on sponsors.

It is also important to determine whether different BMI classifications for obesity should be used depending on the subject's race, but more data is still needed to define specific cutoff levels.

In the meantime, model-informed drug development approaches can still be used to support a new dosing regimen that is not directly tested in clinical trials, and the incorporation of these tools should be achievable at a limited cost.

Conclusions

Obesity is associated with a plethora of pathophysiological changes that make it difficult to consider obese individuals as healthy volunteers. There is a myriad of obesity effects that have an impact on parameters such as pharmacokinetics, safety and tolerability, and they vary greatly depending on the specific drug or Investigational Product being studied/used. Therefore, it seems prudent to conclude that obese individuals should be excluded from early phase clinical trials where the main objectives are safety and tolerability assessment and PK characterization in healthy individuals.

However, the lack of specific regulations and guidance from regulatory agencies up to this point have led us to the current state of affairs where pharmacokinetic investigations targeting obese subjects are usually not implemented or even considered, and where obese patients remain poorly represented throughout development. New initiatives are needed to address this shortcoming and require early phase trials to be carried out in obese individuals for those drugs where this need is predicted by tools such as in silico modeling and population pharmacokinetic analysis (PopPK).

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CONTACT US

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